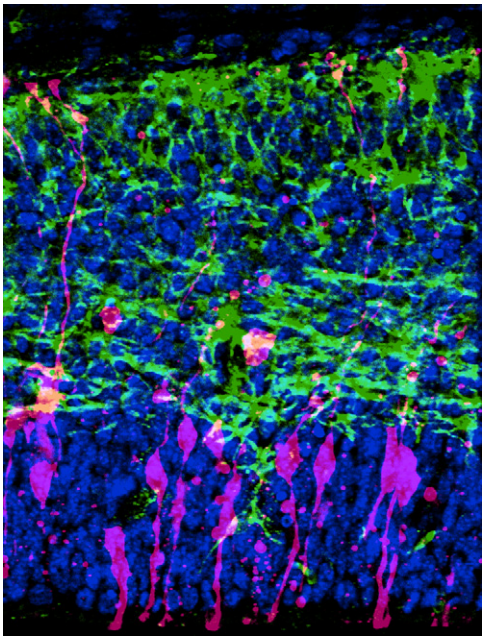
In This Issue

Silhouette of Cells



PAGE 1243

Cell cycle markers with capability to localize in both the nucleus and cytoplasm in the S/G_2/M phases and distinguish between different processes are powerful tools for cellular biologists. Here, Sakaue-Sawano et al. developed a fluorescent probe for exploring the cell cycle based on ubiquitin-mediated proteolysis. The probe represents a protein fusion between a fluorescent protein and a ubiquitination domain of human Geminin, a direct substrate of APC^{Cdh1} E3 ligase that is active in the late M and G_1 phases. The probe was applied to reveal the morphology of individual cells that have undergone DNA replication, thus enabling the monitoring of cell growth relative to differentiation. The study culminated in outlining the silhouette of neural progenitor cells in S/G_2/M phases in the developing cerebral cortex. (Figure credit: Sakaue-Sawano et al.)

Fucose-Specific Lectin LecB Interrupts the Film

PAGE 1249

Pseudomonas aeruginosa is an opportunistic human pathogen that is a primary cause of death in immunocompromised and cystic fibrosis patients. There is an urgent need to develop new therapies against this pathogen because it exhibits multiantibiotic resistance. One of the mechanisms *P. aeruginosa* uses to evade drug molecule attacks is the formation of biofilms, which represents an enduring barrier to antibiotic penetration and decreases treatment efficiency. In this paper, Johansson et al. developed potent ligands, in the form of multivalent glycopeptide dendrimers, against LecB, a carbohydrate-binding protein produced by *P. aeruginosa*. These dendritic ligands effectively inhibit biofilms formed by various pathogenic strains of *P. aeruginosa*, and the study suggests LecB as a viable target for further drug design.

Iron Cylinder DNA Binding Action

PAGE 1258

The cisplatin family of drugs are currently used for treatment of various types of cancers and represent quintessential metal-based therapeutics. Herein, Hotze et al. investigate a different type of potential metal-based drug, a supramolecular iron cylinder, and its effect on cellular proliferation. Similarly to cisplatin, the cylinder reduced mitochondrial activity, inhibited the cell cycle, and increased cell death by apoptosis. However, in stark contrast to existing anticancer drugs, like cisplatin, the cylinder was not genotoxic. Therefore, design of different metal complexes with potential anticancer properties in the absence of the genotoxicity may represent a significant step towards therapeutic advancement.

Fluoride Ion and Enzyme that Can Make It Happen

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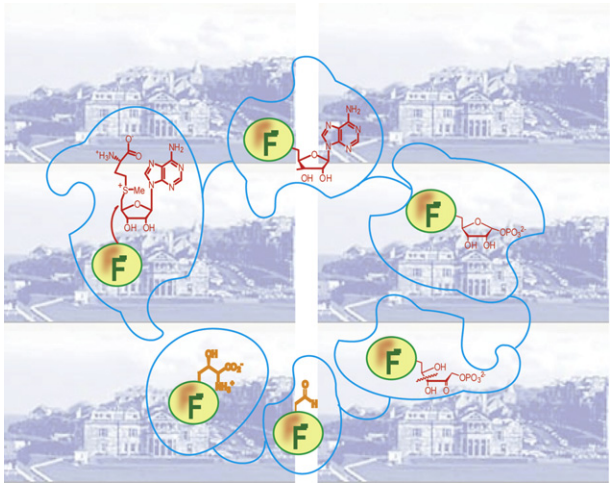


On one hand, fluoride ion is rarely encountered as a substrate in enzymology. But, on the other hand, the ability to enzymatically generate a fluorinated amino acid from fluoride ion has potentially large biotechnological significance. Therefore, the paper by Deng et al. reporting that fluoride ion is converted to the amino acid/antibiotic 4-fluorothreonine in a biotransformation involving five enzymes is exciting. The investigated biotransformation route validates the biosynthetic pathway to 4-fluorothreonine in the bacterium *Streptomyces cattleya* and demonstrates the power of the fluorinase enzyme to initiate C-F bond formation for organofluorine synthesis. (Figure adapted from file provided by Deng et al.)

Mammalian Cell Surface Display

PAGE 1277

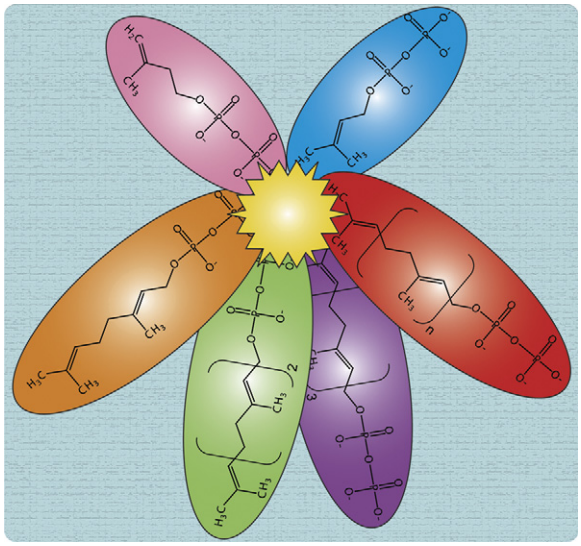
The use of high-throughput screening (HTS) platforms is becoming an indispensable strategy for optimizing enzyme properties via enzyme engineering and directed evolution. Chen et al. now describe a HTS procedure to alter or improve the properties of enzymes based on the expression of the enzyme on the surface of mammalian cells and stable retention of fluorescent reaction products in the cells. A key advantage of this methodology is the ability to link enzymatic activity to the genetic makeup of individual enzyme molecules. This screening methodology should greatly facilitate investigation and modification of the biological activity of eukaryotic enzymes, including those that depend on diverse post-translational modifications for their activity.

Enigmatic Bacterial ATPase YjeE

PAGE 1287

The genomics effort has uncovered many proteins that are good candidate targets for antimicrobials; however, these proteins must first be characterized functionally. Normally, information on gene function comes from forward genetics, "omics" technologies, and bioinformatics. So far these approaches have not been successful in assigning a cellular function for the broadly distributed *Escherichia coli* ATPase *yjeE*. In this study, Mangat and Brown take a chemical genetic approach, whereby molecules with diverse mechanisms of action were used to probe the transcriptional regulation of *yjeE*. This led to the revelation of the first informative phenotype for YjeE, namely, dispensability under anaerobic conditions.

Ambiguous Enzyme: Parasite's Achilles Heel



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Cryptosporidium parvum is a causative agent of intestinal, tracheal, or pulmonary cryptosporidiosis and is one of the most important waterborne pathogens in developed countries. Artz et al. identified a nonspecific enzyme in *C. parvum*, that produces a range of isoprenoid products of different lengths rather than a single specific product, as most enzymes do. This enzyme, determined to be a nonspecific prenyl synthase, can be inhibited at low nanomolar concentrations by nitrogen-containing bisphosphonates. These compounds also inhibit the development of the parasite at low micromolar concentrations, which is a promising result since bisphosphonates are well characterized and already in clinical use. (Figure credit: M. Kostic)

S-nitrosylated Proteins Reveal Their Stability

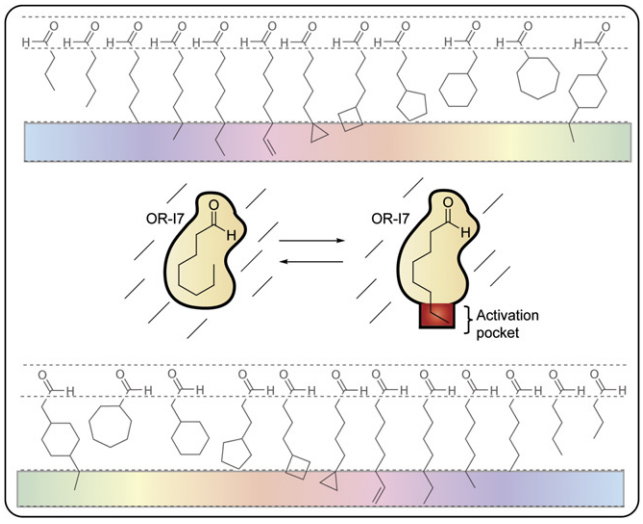
PAGE 1307

Nitric oxide (NO) regulates protein function by *S*-nitrosylation of cysteine residues to form nitrosothiols. Nitrosothiols are highly labile and are likely to be degraded by cytosolic reducing agents. Paige et al. now systematically examine the reactivity of over 100 protein nitrosothiols using a high-throughput proteomic screen. Although most nitrosothiols in proteins were rapidly degraded by reducing agents, a subset formed highly stable nitrosothiols. These proteins appear to undergo conformational changes that shield the nitrosothiol from reducing agents. The data identify a previously undescribed class of NO targets that form stable nitrosothiols and can remain *S*-nitrosylated in the absence of NO synthesis.

Sensing the Chemical Space of Airborne Molecules

PAGE 1317

Peterlin et al. explore the processes of activation and antagonism of a representative G-protein-coupled olfactory receptor (rat OR-I7) as a function of the conformation of its primary odorant (octanal). Odorant conformation was found to be an important determinant of activity potency and type, as certain conformationally restricted 8 carbon octanal analogs were more potent agonists than octanal, while others antagonized receptor activation. Screening >1000 olfactory sensory neurons provided evidence that odorant conformation is a general determinant of aldehyde receptor activation. Thus, odorant receptors, which have evolved to sense chemical space of airborne molecules, interpret chemical space through odorant conformation and functional group identity. (Figure adapted from Peterlin et al.)



Voilà, the Biosynthesis of Radicicol

PAGE 1328

Fungal polyketides with the resorcylic acid lactone (RAL) scaffold are of interest for the treatment of cancer and neurodegenerative diseases, stimulation of growth of livestock, and enhancement of plant thermotolerance. Specific inhibition of the chaperone Hsp90 by the RAL radicicol leads to a combinatorial blockade of cancer-causing pathways. Wang et al. identify clustered genes for radicicol biosynthesis from the endophytic fungus *Chaetomium chiversii*. Gene disruptions and isolation of the produced RALs identified a cluster-specific regulator, a reducing and a nonreducing polyketide synthase that collectively synthesize the radicicol polyketide core, and a flavin-dependent halogenase and a cytochrome P450 epoxidase involved in radicicol tailoring.

